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CITATION:

OHTOSHI, EIICHI ...[et al]. Effect of Interruption of Hepatic Artery on Liver Regeneration. 日本外科宝函 1977, 46(6): 681-688

ISSUE DATE:

1977-11-01

URL:

<http://hdl.handle.net/2433/208232>

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## Effect of Interruption of Hepatic Artery on Liver Regeneration

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Received for Publication Sept. 13, 1977

### Summary

The hepatic artery was interrupted immediately, 7 and 14 days after 70 per cent hepatectomy in dogs to investigate the effect of the hepatic artery on liver regeneration.

1. Almost all the dogs survived for more than 3 days after the interruption of the hepatic artery following 70 per cent hepatectomy, without administration of any antibiotics.

Survival rates at 2 weeks after hepatic dearterialization were 80 per cent when the hepatic artery was interrupted simultaneously with 70 per cent hepatectomy, and 60 and 56 per cent when the hepatic artery was interrupted 7 and 14 days after 70 per cent hepatectomy, respectively.

2. The remnant liver showed no serious changes on regeneration and function when the hepatic artery was interrupted immediately and 7 days after 70 per cent hepatectomy, but regeneration rate was the lowest in the all experimental groups when the hepatic artery was interrupted 14 days after 70 per cent hepatectomy.

From the present experiment, it was revealed that arterial blood supply is most important on hepatic regeneration and maintenance of the remnant liver after 2 weeks following 70 per cent hepatectomy in dogs.

### Introduction

The liver is supplied with blood flow from both the hepatic artery and the portal vein. Usually dogs tolerate well an acute interruption of portal inflow when portal-systemic anastomosis is constructed (Eck, 1877 ; Elman and Cole, 1934), but ligation of the hepatic artery is followed by serious complication (Graham and Cannel, 1933). In 1949, Markowitz, Rappaport and Scott found that large doses of penicillin brought some reduction of high mortality rate associated with an abrupt interruption of the hepatic artery in normal dogs, and suggested that this dearterialization of the liver would be applicable for the treatment of primary carcinoma of the liver.

While a variety of experimental approaches through the years has been made to elucidate the portal blood factors thought to control liver regeneration following partial hepatectomy

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Key words : 70 per cent hepatectomy, Interruption of the hepatic artery, Liver regeneration, Regeneration rate, Survival rate, Remnant liver

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(Mann, 1940 ; Child et al., 1953 ; Price et al., 1972 ; Starzl et al., 1973), the role of the hepatic artery on regeneration of the canine liver is poorly understood (MIZUMOTO et al., 1970).

In the present experiment, the hepatic artery was interrupted at different times following 70 per cent hepatectomy in dogs without administration of any antibiotics, to examine the role of the hepatic artery flow on liver regeneration.

### Materials and methods

Forty-four adult mongrel dogs weighing 8 to 16 kilograms were used under intravenous anesthesia of Nembutal of 25 mg per kilogram body weight. The abdomen was entered through a midline incision and four lobes of the liver (the left lateral, left central, quadrate and right central lobes), about 70 per cent of the entire liver, were removed. The arterial flow into the remnant liver was interrupted by ligation and division of the common hepatic artery, gastroduodenal artery, right gastric artery and proper hepatic artery, with dissection of all attachments to near organs except bile duct and portal vein (Fig. 1).

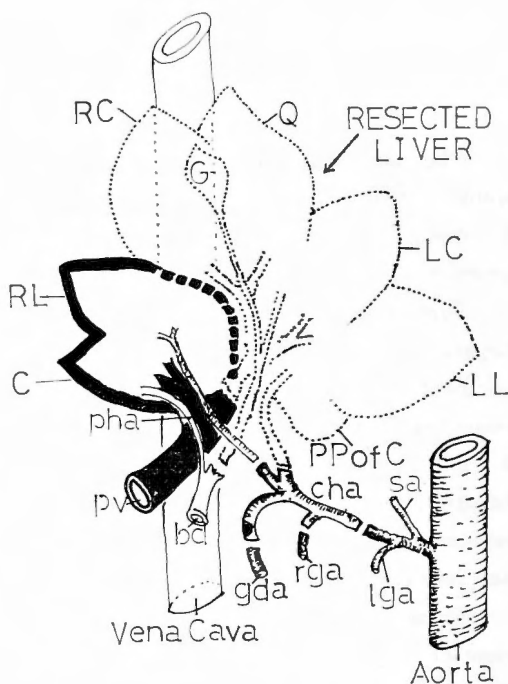
Experimental animals were divided into 4 groups, according to the interval between 70 per cent hepatectomy and the interruption of the hepatic artery, as follows.

**Control group** (13 Dogs) : 5 dogs underwent 70 per cent hepatectomy alone, and the other 8 dogs laparotomy with dissection around the hepatic artery as a sham operation 7 or 14 days after 70 per cent hepatectomy. The remnant liver was supplied with blood flow both the portal vein and the hepatic artery.

**Group A** (10 Dogs) : The hepatic artery was interrupted simultaneously with 70 per cent hepatectomy. The remnant liver was supplied with portal venous flow alone.

**Group B** (5 Dogs) : 7 days after 70 per cent hepatectomy the hepatic artery was interrupted. Therefore the remaining liver had a dual blood supply during the first week and it had only portal venous flow thereafter.

**Group C** (16 Dogs) : 14 days after 70 per cent hepatectomy the hepatic artery was



**Fig. 1.** 70% Hepatectomy and Interruption of the Hepatic Artery,  
C, Caudate ; RL, Right lateral ; RC, Right central ; Q, Quadrate ; LC, Left central ; LL, Left lateral ; PP of C, Papillary process of caudate ; pv, portal vein ; bd, bile duct ; pha, proper hepatic artery ; sa, splenic artery ; gda, gastroduodenal artery ; rga, right gastric artery ; lga, left gastric artery ; cha, common hepatic artery.

interrupted. Therefore the remnant liver was maintained by a dual blood supply during the first 2 weeks and it had only portal venous flow thereafter.

500 ml of 5 per cent glucose was injected intravenously for the first 3 postoperative days and then a regular kennel diet was given ad libitum. None of antibiotics was administered.

Survival rate was calculated from survivors for more than 2 weeks after the interruption of the hepatic artery.

When the experimental animals were sacrificed 4 weeks or more after 70 per cent hepatectomy, 100 ml of Micropack, the radiopaque material, were injected into the abdominal aorta ligated above the diaphragm and below the renal vessels to take hepatic angiography, then the remining liver was removed and weighed.

The regeneration rate of the remnant liver was calculated by the following formula of GRINDLAY and BOLLMAN in 1952; subtraction of the calculated weight of the original remnant from the weight at necropsy is divided by the calculated weight of the original remnant and multiplied by 100.

For blood chemical analysis, total bilirubin, total protein, alkaline phosphatase, GPT and GOT in the serum were measured at intervals.

Histological changes of the liver were observed by hematoxylin-eosin stain 4 weeks after 70 per cent hepatectomy.

### Results

*Control group* : All of the 13 dogs tolerated well 70 per cent hepatectomy (Table I). 5 of these, sacrificed 2 weeks after 70 per cent hepatectomy, showed  $108 \pm 10$  per cent regeneration rate of the remnant liver (Table II), being twice the weight of the remnant estimated from the weight of the resected liver lobes. As for the other 8 dogs that underwent the sham operation 7 or 14 days after 70 per cent hepatectomy and were sacrificed 4 weeks after the hepatectomy, the regeneration rate was  $220 \pm 24$  per cent. In the remnant liver of all 8 dogs the hepatic artery was clearly demonstrated by the hepatic angiography.

*Group A* : All of the 10 dogs survived for more than 3 days, but 2 died of peritonitis

Table I. Survival Rate After Interruption of Hepatic Artery and 70% Hepatectomy

70% hepatectomy	Interruption of hepatic artery	Intervals between two operations	No.	No. of survivor	
				3 days or more	14 days or more
+	+	Simultaneously	10	10 (100%)	8 (80%)
+	—		10	10 (100%)	10 (100%)
+	+	7 days later	5	5 (100%)	3 (60%)
+	—	7 days later #	4	4 (100%)	4 (100%)
+	+	14 days later	16	15 (94%)	9 (56%)
+	—	14 days later #	4	4 (100%)	4 (100%)

# sham operation

Table II. Liver regeneration 2 weeks after 70% hepatectomy (Control group)

Body weight (kgm)	Liver removed (gm)	Liver weight at autopsy (gm)	Regeneration rate (per cent)	Causes of death
9.0	230	200	102	sacrify
9.0	170	140	92	sacrify
9.0	200	190	121	sacrify
9.0	230	210	112	sacrify
10.0	200	180	109	sacrify
Mean±s. d.	9±1	206±23	184±25	108±10

Table III. Liver regeneration 4 weeks after 70% hepatectomy

With sham operation (Control group)

Body weight (kgm)	Liver removed (gm)	Liver weight at autopsy (gm)	Regeneration rate (per cent)
10.0	250	320	200
11.0	220	330	250
11.0	200	270	214
14.0	300	450	250
9.0	210	250	178
11.0	200	280	225
12.0	290	410	230
12.0	220	290	208
Mean±s. d.	12±2	237±37	325±66
			220±24

With interruption of hepatic artery simultaneously (Group A)

10.0	180	240	212
10.0	180	230	199
10.0	210	250	181
11.0	210	295	228
14.0	240	300	194
12.0	140	225	275
16.0	230	285	188
Mean±s. d.	12±3	199±32	261±30
			211±30

With interruption of hepatic artery 7 days later (Group B)

15.0	270	420	260
14.0	210	270	200
10.0	200	250	191
Mean±s. d.	13±2	227±31	314±76
			217±31

With interruption of hepatic artery 14 days later (Group C)

11.0	300	280	119
10.0	280	270	125
14.0	290	310	150
10.0	180	140	82
8.0	160	145	116
Mean±s. d.	11±2	242±60	229±72
			119±22

at the 7th postoperative day. The remaining 8 (80 per cent of all) survived for more than 2 weeks and seven were sacrificed 4 weeks and one 8 months after 70 per cent hepatectomy simultaneously with the interruption of the hepatic artery. Regeneration rate at 4 weeks after the hepatectomy was  $211 \pm 30$  per cent, showing the development of collateral vessels to the remnant liver on hepatic arteriography.

*Group B* : All of the 5 dogs survived for more than 3 days following the abrupt interruption of the hepatic artery 7 days after 70 per cent hepatectomy, but 2 died of peritonitis 4 and 5 days after the second operation. The remaining 3 (60 per cent of all in this group) survived for more than 2 weeks and were sacrificed 4 weeks after 70 per cent hepatectomy. The regeneration rate was  $217 \pm 31$  per cent (Table III). Hepatic angiography showed no clear demonstrable collateral arterial vessels into the remaining lobes 4 weeks after 70 per cent hepatectomy in all 3 dogs.

*Group C* : One out of the 16 dogs died of hepatic coma at the second postoperative day and 15 survived for more than 3 days, but 6 died of peritonitis or emaciation within one week after the second operation. The other 9 dogs survived for more than 2 weeks and five were sacrificed 4 weeks, three 6 weeks and one 8 weeks after 70 per cent hepatectomy, respectively. Then the survival rate was 56 per cent (Table I). The regeneration rate at 4 weeks after the hepatectomy was  $119 \pm 22$  per cent, being almost equal to the rate at 2 weeks after 70 per cent hepatectomy alone in the control group (Table II, III). Furthermore, the regeneration rate at 6 weeks after the hepatectomy was  $115 \pm 13$  per cent (Table IV). Hepatic angiography did not show clearly the hepatic artery and its branches 4 weeks after 70 per cent hepatectomy in all 5 dogs but thin shadow in the remnant liver of 3 dogs 6 weeks after 70 per cent hepatectomy.

**Table IV.** Liver Regeneration 6 weeks after 70% hepatectomy

With interruption of hepatic artery 14 days later (Group C)

	Body weight (kgm)	Liver removed (gm)	Liver weight at autopsy (gm)	Regeneration rate (per cent)
	10.0	210	200	122
	12.0	250	240	124
	9.0	190	160	97
Mean $\pm$ s. d.	$11 \pm 2$	$217 \pm 25$	$200 \pm 33$	$115 \pm 13$

*Histological findings* : No remarkable changes were observed histologically in group A, but in group B the liver cells around central veins showed remarkable atrophy with slight dilatation of the central veins and portal venous branches. The changes in group C consisted of extensive centrilobular atrophy and foci of liver cell degeneration in the central zones, with dilatation of the hepatic and portal venous branches within the liver 4 weeks after 70 per cent hepatectomy.

*Liver function test* : There was an elevation of serum alkaline phosphatase during the

first week following the interruption of the hepatic artery and then it returned to normal level in group A and B. However, it continued to elevate thereafter in some dogs of group C. Changes of total bilirubin and total protein, GPT and GOT in the serum showed no marked differences among the experimental groups.

### Discussion

It has been reported that the liver has a great capacity to regenerate, following partial hepatectomy, and that the regeneration is completed in 6 to 10 weeks in dogs (FISHBACK, 1929 ; CHILD et al., 1953). In our experiment, the weight of the remnant liver was approximately the estimated original total liver weight, about 4 weeks after 70 per cent hepatectomy. On the other hand, an increase of DNA synthesis in the remaining hepatic cells after 70 per cent hepatectomy in dogs occurs during the first five postoperative days and is the greatest on the third and fourth days (SIGEL et al., 1965).

In the present study, the effect of the interruption of the hepatic artery on liver regeneration was investigated for 2 weeks after 70 per cent hepatectomy.

Although ligation of the hepatic artery results in death of normal dogs due to liver necrosis within 3 days (HUGGINS and POST, 1937), the interruption of the hepatic artery simultaneously with hemihepatectomy has no serious effect on the subsequent regeneration and function of the remaining liver (MIZUMOTO et al., 1970) and the regenerated liver tolerates well the interruption of the hepatic artery 8 to 10 weeks after 40 per cent hepatectomy (NOMURA, 1965).

In the present experiment, all the dogs survived for more than 3 days after 70 per cent hepatectomy simultaneously with the interruption of the hepatic artery and the survival rate of more than 2 weeks was as high as 80 per cent (Table I) with good regeneration, showing that the interruption of the hepatic artery immediately after 70 per cent hepatectomy has less influence on maintenance of liver viability, because of the increased portal flow into the remnant liver. However, when the hepatic artery was interrupted 2 weeks after 70 per cent hepatectomy, the regeneration rate 4 weeks after the hepatectomy was lower than that of group A (Table V) and it is almost the same as that of 2 weeks after 70 per cent hepatectomy alone in the control group, showing no increase in liver weight following the interruption of the hepatic artery, with a slight development of

Table V. Liver regeneration 4 weeks after 70% hepatectomy

Associated operation	No.	Body weight (kgm)	Liver removed (gm)	Remnant liver at autopsy (gm)	Regeneration rate (per cent)
Sham operation	8	12±2	237±37	325±66	220±24
Interruption of hepatic artery simultaneously	7	12±3	199±32	261±30	211±30
Interruption of hepatic artery 7 days later	3	13±2	227±31	314±76	217±31
Interruption of hepatic artery 14 days later	5	11±2	242±60	229±72	119±22

collaterals and dominant histological changes of degeneration and atrophy of liver cells.

During early periods after 70 per cent hepatectomy, the remnant liver may be supplied with an increase of portal blood flow and tolerates well the interruption of the hepatic artery. However, since the remnant liver may regenerate about twice in weight and portal flow per liver weight approaches normal rate 2 weeks after 70 per cent hepatectomy, the remnent liver could not tolerate well the interruption of the hepatic artery and a decrease of blood flow after 2 weeks following hepatectomy. On the other hand, to develop effective collaterals into the remnant liver it needs more than 2 weeks after the interruption of the hepatic artery in the canine liver (POPPER et al., 1954 ; JEFFERSON et al., 1956 ; URABE, 1959). Therefore the interruption of the hepatic artery 2 weeks after 70 per cent hepatectomy has a serious effect on subsequent regeneration and function of the remaining liver, due to decrease of effective blood flow.

These findings revealed that arterial blood supply is most important on hepatic regeneration and maintenance of liver function after 2 weeks following 70 per cent hepatectomy in dogs.

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## 和文抄録

## 肝切除と肝動脈遮断

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大 歳 栄 一, 水 本 龍 二, 本 庄 一 夫

肝切除後残存肝に対する肝血行の変動の効果については, Mann 以来, 主として門脈血流の遮断により肝再生が抑制され, 残存肝の萎縮を招くことが指摘されているが, 肝動脈血流の遮断については, 1970年 Mizumoto らが, 犬肝50%肝切除後ペニシリン投与下で, 残存肝への肝動脈流入を完全に遮断しても犬は長期生存し, 残存肝の再生も良好で肝壊死により死亡するものがないことを明らかにし, 門脈血行動態の研究から, これを残存肝に全門脈血が流入するための相対的肝血流量の増加のためと考えている.

本研究では, 更に残存肝の肝再生過程における肝動脈血流の意義を明らかにするため, 犬の肝70%切除直後, 1週目, 2週目に肝動脈遮断を行ない, 残存肝の肝再生過程に及ぼす効果を生存率, 再生率, 組織像, 動脈造影像, 血液生化学的成績について比較検討し, 主として次の結果を得た.

1) 肝広範切除後の肝動脈遮断では, ほぼ全例3日

以上生存するが, 2週目の生存率では肝切除肝動脈同時遮断群が82%であったのに対し, 肝切除後1週目肝動脈遮断群が60%, 肝切除後2週目肝動脈遮断群が56%と不良であった.

2) 肝重量の変化による肝切除後4週目の再生率の比較では, 肝切除後2週目肝動脈遮断群が最も不良で, 他の群は70%肝切除のみを行なった群に近い値を示し, 肝動脈遮断の影響は少なかった.

即ち, 犬では肝切除後2週目の回復過程で, 肝動脈血流の意義が最も重要であると考えられた. また動脈造影像や組織学的変化も, ほぼこの成績を支持する結果であった.

以上の結果より, 肝広範切除後の肝再生の上で, 動脈血を最も必要とする時期は, 犬では肝切除後2週目以後の残存肝の肝再生が進行した時期であり, この時肝動脈遮断を行なうと, 肝への影響が最も大きいことが明らかとなった.